REMARKS

Reconsideration and withdrawal of the rejections of the claimed invention is respectfully requested in view of the amendments, remarks and enclosures herewith, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1, 3, 4, 7 and 9-13 are still pending in this application. No new matter has been added by this amendment.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

II. THE 35 U.S.C. 112, 1st PARAGRAPH REJECTION HAS BEEN OVERCOME

Claims 1, 3, 4, 7 and 9-13 were rejected as allegedly lacking adequate written description for not showing possession of the invention as relating to salt forms of the active compound. This rejection is in error as it is well known that possession of the invention need not be shown by *ipsis verbis* support.[1] The recitation of salt forms of the active compounds is well within the scope of the invention initially described, i.e. "derivatives thereof".

As noted by the Examiner, acid addition salts were specifically mentioned in the specification (see paragraph [0003] of the publication of the specification). No evidence was presented to show why one of ordinary skill in the art would not have deemed the applicant to be in possession of salt forms of active agents especially given the advanced state of the art with regard to salt formation of active ingredients (see e.g. *Handbook of Pharmaceutical Salts – Properties, Selection and Use*, editors P. Heinrich Stahl and C.G. Wermuth, publ. Helvetica Chimica Acta, 374 pages (2002) – ISBN: 3906390268.).

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[1] The invention claimed does not have to be described in ipsis verbis in order to satisfy the description requirement of §112. *In re Lukach*, 442 F.2d 967, 969 (CCPA 1971)(citations omitted). Instead, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question. *In re Edwards,* 568 F.2d 1349, 1351-1352, 196 USPQ 465, 467 (CCPA 1978).

III. THE 35 U.S.C. 112, 2nd PARAGRAPH REJECTION HAS BEEN OVERCOME

Claims 1, 3, 4, 7 and 9-13 were rejected as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention for using the phrase "and salts thereof".

The applicants' response to the 1st paragraph rejection is incorporated by reference here; salt forms of active ingredients are well known to those of skill in the art and the skilled artisan would be apprised of the metes and bounds of the invention and would recognize this phrase as being applicable to each of the elements recited in the Markush group.

IV. THE 35 U.S.C. 103(a) REJECTION HAS BEEN OVERCOME

A. Claims 1, 3, 4 and 12 were rejected as allegedly being obvious by Zhang et al. (U.S. Patent 6,264,981 – **"Zhang"**) **in view of** Patel et al. (U.S. Patent 6,248,363 – **"Patel"**); Weete et al. (U.S. Patent 5,703,255 – **"Weete"**), *Steadman's Medical Dictionary* (Lippinicott & Wilkins, 2000; accessed online 5/13/2008 – **"Steadman"**); and by Raisch et al. (Ann. Pharmacother., 2002 February; 36(2): 312-321 – **"Raisch"**). The applicants request reconsideration of this rejection in light of the previous arguments presented in the response of 19 March 2009 and the applicants further comments below as the comments in the "Response to Arguments" section appears to reveal a lack of understanding of the technology behind the claimed invention.

1. Combination of references does not direct one of ordinary skill in the art to the applicants' element of (1) "in a phosphatidylcholine fraction in which the fatty acid residues *are at least 90% saturated*"

Once *prima facie* obviousness is established by the Examiner, the applicants must rebut the presumption of obviousness. However, this is easily accomplished by the applicants as the initial *prima facie* holding of obviousness is based on as yet unchallenged positions set forth by the Examiner and merely requires "a showing of facts supporting the opposite conclusion and may relate to any of the *Graham* factors including the so-called secondary considerations." *In re Piasecki,* 745 F.2d 1468, 1472 (Fed. Cir. 1984).

When the applicants present a reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, ***the entire merits of the matter are to be reweighed***. *In re Hedges*, 783 F.2d 1038, 1039, 228 USPQ 685, 686 (Fed. Cir. 1986).[2]

With regard to the equivalency of lecithin and phosphatidylcholine, the applicants note that the specific element of the applicants' claimed invention which refers to phosphatidylcholine refers to fatty acid residues of the phosphatidylcholine fraction are at least 90% saturated. Moreover, with regard to the point of equivalency for lecithin and phosphatidylcholine, the applicants' arguments and evidence only appeared to be considered for their "knockdown ability". At best, one of ordinary skill in the art when confronted with the evidence provided by the Examiner and the applicants would have found the positions to be in equipoise, if not in favor of the applicants. However, being in equipoise is insufficient to establish or maintain a rejection based on obviousness; the rejection must be supported by a preponderance of the evidence ("more likely than not").

The applicants also point to one of the Examiner's own references which supports the position that lecithin and phosphatidylcholines are different. Patel refers to "hydrogenated lecithin" (col. 31, line 23) and "phosphatidylcholine" (col. 31, line 38), but NOT to hydrogenated phosphatidylcholine. Further evidence that phosphatidylcholine is not presumed to be equivalent to hydrogenated phosphatidylcholines can be found from the entry of *Fiedler Encyclopedia of Excipients for Pharmaceuticals, Cosmetics and Related Areas (6th edition)*[3] for Epikuron (E145 has a minimum of 45% phosphatidylcholine whereas Epikuron 200 is hydrogenated phosphatidylcholine) – copy attached to the end of this response.

The applicants also provide further evidence that the term phosphatidylcholine is different from lecithin from RÖMPP Online version 3.4

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2 "When prima facie obviousness is established and evidence is submitted in rebuttal, the decision-maker ***must start over***. . . . ***An earlier decision should not***, as it was here, be considered as set in concrete, and applicant's rebuttal evidence then ***be evaluated only on its knockdown ability***. Analytical fixation on an earlier decision can tend to provide that decision with an undeservedly broadened umbrella effect. Prima facie obviousness is a legal conclusion, not a fact. Facts established by rebuttal evidence must be evaluated along with the facts on which the earlier conclusion was reached, ***not against the conclusion itself***. . . . [A] final finding of obviousness may of course be reached, but such finding will rest upon evaluation of all facts in evidence, uninfluenced by any earlier conclusion reached by an earlier board upon a different record." *In re Rinehart*, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (CCPA 1976).

3 Copy of *Fiedler* is provided as part of an Information Disclosure Statement filed concurrently with this response

(http://www.roempp.com/prod/index1.html) – copy to attached to the end of this response – the entry for "Phosphatidylcholin" (German for phospharidylcholine) includes the section "Verwendung von Lecithin" (Composition of Lecithin) which states in part "...So-called Soya-Lecithin consists of Phosphatidylcholine (40-50%), Phosphatidylethanolamine (about 10%), Phosphatidyinositol (about 5%), Phosphatidylserin (about 1-2%) as well as Sterols and Fats and Oils."[4]

Clearly, the weight of the evidence of record supports the position that lecithins are not equivalent to phosphatidylcholines and that hydrogenated phosphatidylcholines are distinct from phosphatidylcholine itself.

To the extent that it could be argued that hydrogenated lecithin would necessarily encompass some hydrogenated phosphatidylcholine, there is no evidence which supports that the fatty acids of the phosphatidylcholine has a degree of hydrogenation which exceeds 90% as in the applicants claimed invention.

In addition, the elements of the applicants claimed invention result in the active compound being dissolved in the lamellar mesophase of the structure formed (see paragraph [0022] of the publication of the specification). Given the nature of formation of lamellar mesophases, one of ordinary skill in the art would not have a reasonable expectation of success that the additional elements within lecithin besides the hydrogenated phosphatidylcholine would result in lamellar mesophase.

2. References relied upon refer to encapsulation of the active ingredient not dissolution of the active ingredient in a lamellar mesophase

The lack of a reasonable expectation of success that the additional elements within lecithin besides the hydrogenated phosphatidylcholine would result in lamellar mesophase is borne out by the fact that the cited references are not related to lamellar phases at all, but the formation of conventional encapsulation to deliver the active compound.

Attached to this response is a copy of "Introduction to Liquid Crystals" from http://barrett-group.mcgill.ca/teaching/liquid_crystal/LC05.htm. The phase diagram on the first page shows a clear delineation between lamellar phases and micelles which is further illustrated

[4] This is an English translation of the original German which read "...Soganannntes Soja-Lecithin besteht aus Phosphatidylcholin (40-50%), Phosphatidylethanolamin (ca. 10%), Phosphatidyinositol (ca. 5%), Phosphatidylserin

by the structural diagrams on the bottom of page 2 (lamellar phase) and page 3 (micelles/spherical vesicles).

The combination of references does not teach or suggest that the active ingredient is dissolved in the lamellar phase nor would there be a reasonable expectation or reason for modifying the encapsulated forms of the cited references to a lamellar phase.

3. For the applicants' claimed invention, the number of references cited in the obviousness rejection is an indicia of non-obviousness

While there is no official limit for the number of references which can be combined in order to establish an obviousness rejection, the as a whole consideration which is required for analysis of the applicants' claimed invention also applies to each reference which is cited in the rejection, i.e. a reference cannot be selected for an isolated teaching to the exclusion of what the entire reference itself teaches.

Situations where multiple references are necessary to establish a *prima facie* case of obviousness usually manifest itself where the claimed invention is broadly drafted or has several Markush-group type elements. However, given the complex nature of the applicants' invention which results in the active compound being dissolved in the lamellar mesophase formed by the combination of a) and b), the number and scope of the claimed elements of the applicants' invention are comparatively narrow. As such, the fact that six (6) references must be relied upon is a clear indicia that the applicants' invention was not obvious; put another way, one of ordinary skill in the art when confronted with the entirety of the teachings of each of the six references would not find it obvious to pick and choose the necessary elements of the applicants' claimed invention without the guide that the applicants claims provide.

B. Claims 1 and 7 were rejected as allegedly being obvious by Zhang et al. (U.S. Patent 6,264,981 – **"Zhang"**) **in view of** Patel et al. (U.S. Patent 6,248,363 – **"Patel"**), Weete et al. (U.S. Patent 5,703,255 – **"Weete"**), and Shen et al. (U.S. Patent 6,255,490 – **"Shen"**). The applicants request reconsideration of this rejection for the following reasons.

(ca. 1-2%) sowie Sterolen und Fetten und Ölen."

C. Claims 1 and 9 were rejected as allegedly being obvious by Zhang et al. (U.S. Patent 6,264,981 – **"Zhang"**) **in view of** Patel et al. (U.S. Patent 6,248,363 – **"Patel"**), Weete et al. (U.S. Patent 5,703,255 – **"Weete"**) and **Cary** (U.S. Patent 6,197,827). The applicants request reconsideration of this rejection for the following reasons.

D. Claims 1 and 10 were rejected as allegedly being obvious by Zhang et al. (U.S. Patent 6,264,981 – **"Zhang"**) **in view of** Patel et al. (U.S. Patent 6,248,363 – **"Patel"**), Weete et al. (U.S. Patent 5,703,255 – **"Weete"**) and Plotnikoff et al. (U.S. Patent 3,706,831 – "**Plotnikoff**"). The applicants request reconsideration of this rejection for the following reasons.

E. Claims 1 and 11 were rejected as allegedly being obvious by Zhang et al. (U.S. Patent 6,264,981 – **"Zhang"**) **in view of** Patel et al. (U.S. Patent 6,248,363 – **"Patel"**), Weete et al. (U.S. Patent 5,703,255 – **"Weete"**) and Serra et al. (*Eur. J. Pharmacol.* 2001 November; 430(2-3): 369-371 – "**Serra**"). The applicants request reconsideration of this rejection for the following reasons.

F. Claims 1 and 13 were rejected as allegedly being obvious by Zhang et al. (U.S. Patent 6,264,981 – **"Zhang"**) **in view of** Patel et al. (U.S. Patent 6,248,363 – **"Patel"**), Weete et al. (U.S. Patent 5,703,255 – **"Weete"**) and Majeti et al. (U.S. Patent 5,599,554 – "**Majeti**"). The applicants request reconsideration of this rejection for the following reasons.

With regard to the rejections of claims 7, 9, 10, 11 and 13, none of the supporting references address the deficiencies of the combination of Zhang, Patel and Weete with regard to claim 1, 3, 4 and 12 and as such should be withdrawn with the withdrawal of the rejection of claim 1.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution. The Commission is authorized to charge any fee occasioned by this paper, or credit any overpayment of such fees, to Deposit Account No. 50-0320.

Respectfully submitted,
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Attachments: *Fiedler Encyclopedia of Excipients for Pharmaceuticals, Cosmetics and Related Areas (6th edition)*, page 568, (2007).
"Introduction to Liquid Crystals" from
http://barrettgroup.mcgill.ca/teaching/liquid_crystal/LC05.htm